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Particulate contaminants of intravenous medications and infusions

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Particulate contamination in small volume parenteral medications has been studied and compared with that found in a selection of large volume infusions. Particle counts in 39 commonly used small volume medications and 7 large volume infusions were performed by an automated light blockage method (HIAC) or by optical microscopy. Based on these results and a random survey of drug therapy of intensive care patients, it is concluded that the contribution of intravenous medications to the total particle load received by such patients is likely to be many times greater than from infusion fluids. Until firm evidence regarding the harmful systemic effects of drug particles is available and the manufacturing regulations adjusted appropriately, final in-line filtration of infusions immediately proximal to the intravenous cannula should be considered when drugs are being given intravenously.

Particles in intravenous medications and infusions arise from two principal sources. Intrinsic contaminants result from manufacture, packaging, transport and storage, whereas extrinsic particles are introduced at the time of drug reconstitution and administration to the patient. Both must be considered potentially harmful (Leong 1982). There is strong evidence incriminating them in infusion phlebitis (Bivins et al 1979; Allcutt et al 1983; Falchuk et al 1985) but their systemic effects have never been adequately studied (Garvan & Gunner 1964; De Luca et al 1975).

Both the British Pharmacopoeia (BP 1980) and United States Pharmacopeia (USP XXI/National Formulary XVI 1985) include precise standards for particles in large volume parenterals (LVPs) but only recently have standards for small volume parenterals (SVPs) been proposed (USP XXI/NF XVI 1985). These are based upon the existing standards for LVPs with the assumption that an average patient will receive 5 SVP doses for every LVP and the number of particles in an SVP should be no more than one-fifth of that contained in an LVP (Pharmacopeial Forum 1983). This assumption takes no account of present levels of particulate contamination in drugs and the decision to introduce the 'one-fifth rule' appears not to have foundation in fact. More importantly, the original LVP standards were set with little firm clinical or experimental evidence for what might be a 'safe' level of particulate contamination, making the new standards even less satisfactory.

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The British Pharmacopoeia has not yet proposed numerical standards and simply states for SVPs '. . . when examined under suitable conditions of visibility, are clear and practically free from particles'. Those for LVPs limit particles larger than 2 μm to 'no more than 500 mL^{-1}' and those >5 μm to '80 mL^{-1}' when counted by the light blockage method (HIAC). A number of studies of particles in small volume medications have shown levels of contamination considerably higher than would be acceptable in LVPs (Pearse et al 1982; Taylor & Spence 1983). Our aim was to determine the number of contaminating intrinsic particles in SVPs and hence their relative importance in terms of total particle load in standard infusion therapy. We therefore planned to examine a wide range of commonly used small and large volume parenterals for particles in various size ranges from 2 μm (the lower limit of automated counting methods) to greater than 40 μm.

METHODS

Parenterals studied

Thirty-nine SVPs and 7 LVPs were analysed. The SVPs included 22 powdered or lyophilized drugs packed in vials or ampoules and 17 drugs in solution supplied in vials, ampoules or bottles. The LVPs were packed in plastic bags, plastic bottles or glass bottles. The range of drugs and infusions is shown in Table 1. Samples were selected from stocks in a large hospital pharmacy and include products from a wide range of major pharmaceutical manufacturers, who had all consented to their products being studied. Two samples from different batch numbers of each product were examined.

Table 1. Drugs and infusions grouped according to principal action.

Small volume parenterals (n = 39)			
Antibiotics	17	Antihypertensive	1
Cytotoxic agents	2	Cardiac drugs	3
Anaesthetics	3	Bronchodilator	1
Analgesics	3	Diuretics	2
Anxiolytic	1	Muscle relaxant	1
Anticoagulant	1	Steroids	2
Antiepileptic	1	X-ray contrast	1
Large volume parenterals (n = 7)			
Crystalloids	4	Plasma expanders	2
Parenteral nutrient	1		

Sample preparation

To reconstitute drugs in vials, the closure ring and cap were carefully removed from the container and the exact volume of the solution recommended by the manufacturer was added via a 0·2 μm rated membrane filter. The cap was replaced and the vial shaken until no visible particles remained. Ampoules containing drugs requiring reconstitution were opened by breaking the neck in the usual way and adding the recommended solution as before via a membrane filter. All manipulations were performed in a laminar flow cabinet.

Particle counting

Particle counting was performed by both an automated light blocking method using a HIAC PC-320 counter, connected to a HIAC D2-60 sensor and automatic bottle sampler (HIAC/Royco Instruments Division) and by optical microscope counting using standard techniques (USP XXI/NF XVI 1985). The HIAC counter was calibrated using latex spheres of a known mean diameter (validated by optical microscope counting) by the half count method (CETOP, RP 94H, 1978). Glassware was cleaned by washing in detergent solution (Decon-90), de-ionized water, propan-2-ol, trichlorotrifluoroethane, propan-2-ol and finally de-ionized water, all of which (except the detergent) were terminally filtered through 0·2 μm rated membrane filters fitted to pressurized dispenser guns. All critical manipulations were performed in a laminar flow cabinet.

To minimize errors resulting from air bubbles, automated particle counting was performed on degassed samples by applying a reduced pressure to the bottle sampling chamber. A background count was carried out using 100 mL of 0·2 μm filtered saline (0·9% NaCl w/v), then the drug sample was added to the saline and particle counting repeated. For optical counting, the drug sample was added to 50 mL of 0·2 μm filtered saline and 25 mL of this was passed through a 0·8 μm rated, black, gridded analysis membrane. This was dried, mounted on a Petri slide and particles in the size range >2, >5, >25 and >40 μm were counted by microscopy using an incident light source.

Scanning electron microscopy and X-ray emission spectrometry

Aliquots of the samples used for particle counting were filtered through 0·8 μm rated membranes. These were dried, mounted on stubbs and gold or carbon coated. They were examined using an ISI40 scanning electron microscope and representative areas photographed. The X-ray fluorescence of the individual particles was recorded using an X-ray emission spectrometer (Model 860, Series 1, Link Systems, High Wycombe, Bucks).

RESULTS

There was wide variation in total particle counts between drugs as well as a marked variation for different batches of the same drug (Fig. 1). Infusion

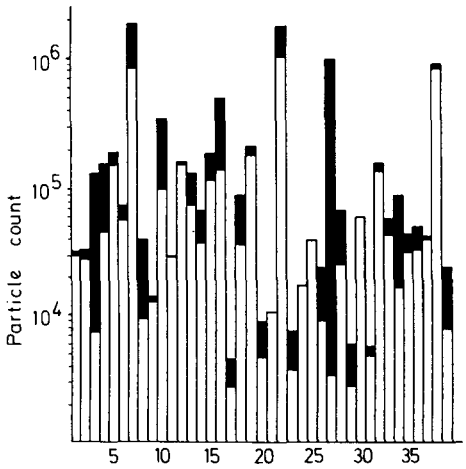

FIG. 1. Numbers of particles larger than 2 μm per dose in the 39 small volume parenteral drugs: (1) ampicillin, (2) azlocillin, (3) benzylpenicillin, (4) cefotaxime, (5) cefoxatin, (6) cefuroxime, (7) cefamandole, (8) cephazolin, (9) cotrimoxazole*, (10) erythromycin, (11) flucloxacillin, (12) sodium fusidate, (13) gentamicin, (14) metronidazole, (15) mezlocillin, (16) tetracycline, (17) tobramycin, (18) cyclophosphamide, (19) doxorubicin, (20) bupivicaine*, (21) fentanyl*, (22) methohexitone, (23) diamorphine*, (24) morphine*, (25) papaveretum*, (26) diazepam*, (27) heparin*, (28) phenobarbitone*, (29) hydralazine*, (30) phentolamine, (31) aminophylline*, (32) digoxin, (33) dopamine*, (34) bumetanide*, (35) frusemide*, (36) pancuronium*, (37) hydrocortisone, (38) methyl prednisolone, (39) meglumine iothalamate*. (* Shows products in snap-open ampoules) open and filled columns represent each of the two batches studied.

fluids had lower levels of contamination but also showed marked variation between products (Fig. 2). The mean (±s.e.m.) particle count >2 μm for medications was $1{\cdot}5 \times 10^5 \pm 5{\cdot}1 \times 10^4$ per sample which was dramatically greater than the mean of 82 ± 50·7 particles mL^{-1} for the 7 infusion fluids ($P < 0{\cdot}001$). As might be expected, the 22 powdered or lyophilized medications contained significantly more particles at $2{\cdot}4 \times 10^5 \pm 8{\cdot}7 \times 10^4$ than that of $2{\cdot}9 \times 10^4 \pm 4{\cdot}5 \times 10^3$ for the 17 drugs in solution ($P < 0{\cdot}05$, Fig. 3). It is thought that antibiotics in particular induce phlebitis by particle contamination (Collins et al 1968), but no significant difference in total counts or counts in any size range was found between antibiotics and other medications (Table 2).

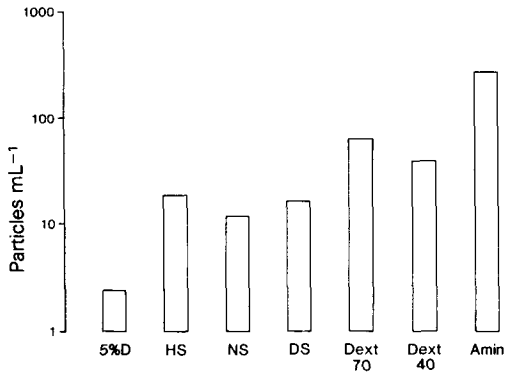

FIG. 2. Particle counts per mL larger than 2 μm for the infusion fluids. The seven fluids tested were 5% dextrose (5%D), Hartmann's solution (HS), normal saline (NS), dextrose saline (DS), dextran 70, dextran 40 and Aminoplex (Amin).

A random survey of 20 patients in the intensive care unit showed they received a mean (±s.e.m.) of 24 ± 1·2 SVP doses per 24 h (range 17–33). If the accompanying LVP therapy were at a maintenance level of 3 L per day then the total intrinsic daily particle load from infusion fluids calculated from our results would be: $82 \times 3000 = 2{\cdot}46 \times 10^5$. From 24 SVP doses a particle load of $3{\cdot}6 \times 10^6$ ($24 \times 1{\cdot}5 \times 10^5$) would be expected, which is 15 times the level from LVPs. These calculations are based on mean counts of intrinsic contaminants measured in drug samples removed from their containers in strictly

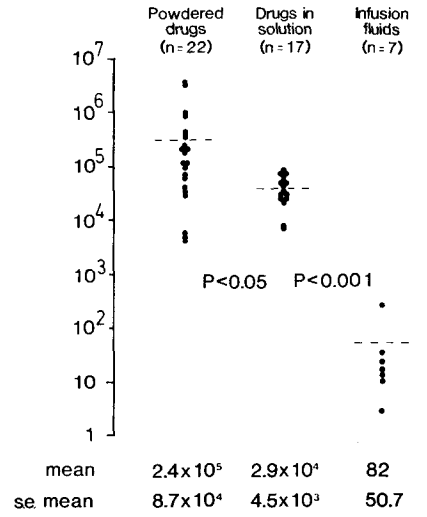

FIG. 3. Comparison of particle counts larger than 2 μm for drugs (particles/sample) packed as powders or in solution and infusion fluids (particles mL^{-1}).

controlled 'ideal' conditions and take no account of the extrinsic particles which would be introduced at the time of administration to patients.

X-ray emission spectrometry of particles on scanning electron micrographs detected many inorganic elements notably calcium, silicon, aluminium, lead and iron which suggests an origin in the manufacture and packaging procedures rather than undissolved drug crystals during reconstitution (Table 3). As an example, the particles and X-ray spectrogram for dopamine is shown in Fig. 4.

DISCUSSION

The very much higher level of particulate contamination in drugs suggests that most patients accumulate considerably greater particle loads from small volume medications than from large volume infusions. As in this study, extensive precautions were taken to reduce extrinsic contamination during reconstitution, the particle levels we have found are likely to be much lower than those administered to patients: Additional particles would inevitably arise from syringes, needles, infusion sets and cannulae (Taylor 1982). In practice, it is likely that intensive care

Table 2. Mean particle counts per dose (±s.e.m.) in four size ranges of the small volume parenterals.

	>2 μm	>5 μm	>25 μm	>40 μm
Antibiotics (n = 17)	$1{\cdot}62 \times 10^5$ $\pm 7{\cdot}74 \times 10^4$	$5{\cdot}19 \times 10^4$ $\pm 3{\cdot}0 \times 10^4$	$3{\cdot}2 \times 10^2$ ±92	67 ±14·5
Other medications (n = 22)	$1{\cdot}36 \times 10^5$ $\pm 7{\cdot}03 \times 10^4$	$6{\cdot}02 \times 10^4$ $\pm 4{\cdot}24 \times 10^4$	$3{\cdot}76 \times 10^2$ ±61	85 ±14·4

Table 3. Elements found in particulate contaminants in order of frequency with percentage of drugs in which they occur.

Calcium	62%	Iron	8%
Silicon	54%	Sodium	5%
Aluminium	44%	Barium	5%
Lead	18%	Titanium	2·5%
Sulphur	10%	Nickel	2·5%

Other elements found in trace quantities in some samples

Chromium	Zinc
Potassium	Vanadium

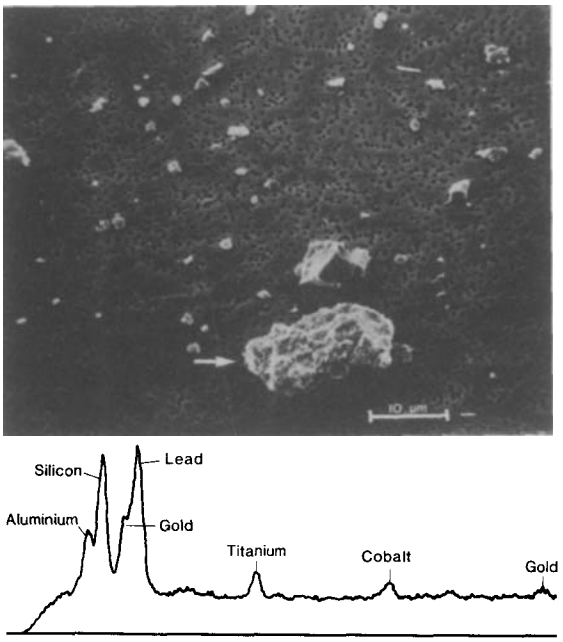

FIG. 4. Scanning electron micrograph of particulate contaminants from dopamine with X-ray spectrometry of arrowed particle.

patients often receive more than 10^7 foreign particles >2 μm per 24 h with their intravenous therapy. We can only speculate on the additional number of particles smaller than 2 μm but on theoretical grounds extrapolating from the number of particles in each size range the number is likely to be very high (Fig. 5). Niden & Aviado (1956) found that experimental injection of a given mass of glass beads produced greater pulmonary dysfunction with smaller particle sizes suggesting systemic effects might be related to surface area rather than size of particles. If so, large numbers of smaller particles would potentially be most worrying.

Assuming it is desirable to reduce this there are two possible approaches. The first is to limit the allowable level of intrinsic particle contamination

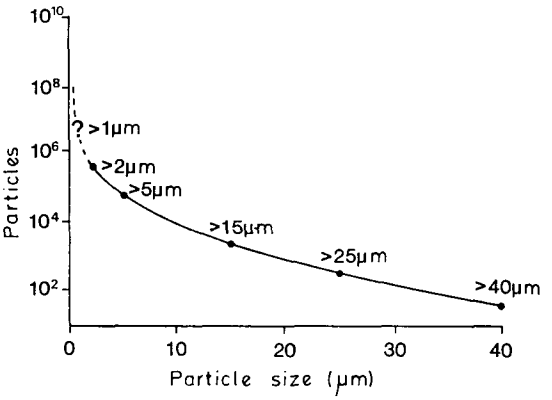

FIG. 5. Particle size plotted against mean numbers in the size ranges. When extrapolated to sizes less than 2 μm which could not be counted accurately the total numbers are probably very high.

whilst at the same time minimizing sources of extrinsic particles. This would appear to be the favoured course of the US Pharmacopeia. Elemental analysis suggests that the majority of intrinsic particles result from leaching and dissolution of the surfaces of glass containers or coatings of rubber closures as well as from later stages of drug manufacturing processes, container filling and closure. Unfortunately, the technology to produce, package and store completely particle-free products on a large scale is not currently available and would be expensive to develop and operate.

An alternative is to reduce both intrinsic and extrinsic contaminants by a terminal in-line filter immediately proximal to the intravenous cannula. Allcutt et al (1983) showed that in-line filtration delayed the onset of infusion phlebitis which is the only well-documented clinical complication of particulate drug contaminants. Since we have shown that most particles are likely to be associated with the administration of multiple small volume parenterals, it seems logical that infusions where drugs are added are most likely to benefit from final in-line filtration. This approach tackles the problem of both extrinsic and intrinsic contaminants and will probably prove to be less expensive than setting standards of manufacture that may be difficult for the pharmaceutical industry to meet.

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